#10
7-16-02
YC

BOX AF
RESPONSE AFTER FINAL REJECTION
EXPEDITED PROCEDURE
EXAMINING GROUP 1610

PATENT
Attorney Docket No. 0606-0019

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Bent HOJGAARD et al.	)	
	)	
Application No.: 09/642,160	)	Group Art Unit: 1615
	)	
Filed: August 21, 2000	)	Examiner: T. WARE
	)	

For: A PHARMACEUTICAL DELIVERY SYSTEM FOR VITAMIN C AND VITAMIN E AND USE OF A COMBINATION OF VITAMIN C AND E FOR PREVENTING OR TREATING CONDITIONS INVOLVING OXIDATIVE STRESS

Assistant Commissioner for Patents
Washington, D.C. 20231

REQUEST FOR RECONSIDERATION AFTER FINAL REJECTION

Sir:

In response to the Final Office Action mailed February 26, 2002, the shortened statutory period for response to which having been extended to July 26, 2002, by the attached Petition for Extension of Time and fee, Applicants respectfully request reconsideration and withdrawal of the rejections set forth in the Final Office Action in view of the following remarks and those of the previous response. Claims 38-73 are pending and under examination in this application.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

I. *Priority*

The Office indicates that a certified copy of the priority document, Danish Patent Application No. 1999 01145, filed on August 20, 1999, has not yet been submitted. Attached hereto is a certified copy of the priority application. Applicants respectfully submit that their claim for priority is now perfected.

II. *Maintained Rejections*

In the Final Office Action, the Office maintains the rejection of claims 38-56 under 35 U.S.C. § 103(a) as unpatentable over Valducci ("the '703 patent"), and claims 57-73 over the '703 patent in view of Sato *et al.* (1993) or Niki (1986). Applicants respectfully traverse these rejections and submit that the present claims are patentable over the cited references, alone or in combination.

Claims 38, 57, and 67 are the only independent claims that are currently pending. Because dependent claims include all of the elements recited in the claims from which they depend, if an independent claim is patentable over a reference or combination of references, all claims that depend from it will likewise be patentable over that reference or those references. Accordingly, Applicants will address the outstanding rejections as they apply to the independent claims only, with the understanding that the arguments are equally applicable to all of the claims that depend from them. Because independent claims 38, 57, and 67 are patentable over the cited references (as discussed below), dependent claims 39-56, 58-66, and 68-73 are patentable as well, and for the same reasons.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

A. The '703 Patent

The Office for the first time specifically identifies Example 10 of the '703 patent as disclosing a composition comprising both vitamin C and vitamin E. (Final Office Action at page 2.) The Office asserts that the composition renders present claim 38 obvious. Applicants respectfully traverse this rejection and submit that the '703 patent does not render claim 38 obvious. Applicants' respectfully submit that their previous response did not address Example 10 of the '703 patent because they were under the belief that the Office was relying on Example 9 of the '703 patent to reject the claims. Applicants will address the disclosure of Example 10 at this time.

The Office notes that, in the composition of Example 10 of the '703 patent, vitamin C is present in an amount within the range recited in present claim 38. The Office recognizes that the composition, while comprising vitamin E, does not comprise vitamin E in an amount within the range recited in present claim 38 (*i.e.*, an amount in the delivery system so as to deliver a daily dose corresponding to 50 mg - 500 mg of α-tocopherol). The Office also recognizes that the '703 patent does not provide any motivation to increase the amount of vitamin C or vitamin E provided in the composition of Example 10.[1] However, the Office asserts that it "would be within the ken of one skilled in the art . . . to provide greater doses of vitamins . . . in someone who is malnourished." (Final Office Action at pages 2-3.) Applicants respectfully submit that

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

[1] Applicants respectfully submit that, contrary to the assertion of the Office on page 3, under the heading "Response to Arguments", Applicants have not argued that the '703 patent provides a motivation to increase the amounts of either vitamin C or vitamin E provided in the '703 patent. It was the Office, not Applicants, that asserted that such a motivation is present in the '703 patent.

the motivation provided by the Office is insufficient to motivate one to select the presently claimed range of vitamin E.

doesn't say what ratio is

Present claim 38 recites a pharmaceutical delivery system for oral delivery of the antioxidants vitamin C and vitamin E **to obtain a controlled ratio between vitamin C and vitamin E** in blood plasma in humans or animals. The controlled ratio recited in claim 38 is a daily dose corresponding to 60 mg - 2 g of vitamin C, and an amount of vitamin E corresponding to 50 mg - 500 mg of α-tocopherol. The specification states that the present invention is based on the notion that a certain ratio between vitamin C and vitamin E is necessary for optimum protection of LDL particles. (See the present specification at page 7, lines 22-24, for example.) Accordingly, in order to render obvious present claim 38, the prior art must recognize the importance of the controlled ratio. See MPEP § 2144.05. Applicants respectfully submit that the art cited by the Office does not recognize this importance.

Thus, it is not sufficient for the Office to simply assert that one would have been motivated to increase the amount of vitamin E in the composition of Example 10. Rather, the Office must show that one would have been motivated to increase the amount of vitamin E from the disclosed amount to an amount within the range recited in claim 38. Applicants respectfully submit that the Office has not shown such a motivation.

In the absence of a showing of motivation to achieve the presently claimed ranges, the Office has failed to set forth a *prima facie* case of obviousness. Therefore, Applicants respectfully request that the Office reconsider and withdraw the rejection of claim 38 under 35 U.S.C. § 103(a) as unpatentable over the '703 patent.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

B. The '703 Patent in View of Sato *et al.* (1993)

The Office maintains its rejection of claims 57 and 67 over the '703 patent in view of Sato *et al.* The Office relies on the '703 patent for the disclosure discussed above. The Office relies on Sato *et al.* for the disclosure that vitamin A [*sic*, E] and vitamin C interact synergistically to decrease oxygen toxicity in oxidative stress situations. Based on these disclosures, the Office asserts that it would have been obvious to one of ordinary skill in the art to treat oxidative stress with the composition of Example 10 of the '703 patent, as modified by the Office to comprise "greater doses of vitamins", "with the motivation of maintaining high concentrations of vitamins C and E". (Final Office Action at page 4.) Applicants respectfully traverse this rejection.

Present claim 57 recites a method of treating oxidative stress disorders and associated diseases and conditions, comprising administering to an individual a combination of vitamin C and vitamin E in sufficient amounts to achieve a concentration of vitamin E in the blood plasma that is at least 20 μmol/liter and a concentration of vitamin C in the blood plasma that is at least 40 μmol/liter, and to a ratio of approximately 1:1 to 3:1, in not more than 8 weeks from the first administration. Claim 67 recites a method of treating oxidative stress disorders and associated diseases and conditions comprising administering to an individual at least one dosage unit per day of a combination of vitamin C and vitamin E in sufficient amounts to raise the concentration of the vitamins in blood plasma sufficiently to treat at least one oxidative stress disorder and to a controlled ratio. The method further recites, among other things, that the method achieves a concentration of vitamin E in the blood plasma of at least 20 μmol/liter, and a concentration of vitamin C in the blood plasma of at least 40 μmol/liter.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Initially, as discussed above, the '703 patent provides no motivation to adjust the concentrations of vitamin C or vitamin E provided in the composition of Example 10 of the '703 patent, for whatever purpose. Furthermore, the general motivation provided by the Office to increase the amount of vitamin E in the composition of Example 10 to maintain "high concentrations of vitamins C and E" is contradicted by the disclosure of Sato *et al.*, which is specifically relied upon by the Office to assert that claims 57 and 67 are obvious.

Sato *et al.* discloses that combinations of α-tocopherol (vitamin E) and vitamin C were effective at improving neuronal survival under oxidative stress. Sato *et al.* discloses that concentrations of 10^{-8} to 10^{-6} (*i.e.*, 10 nM - 1μM) of vitamin E and $2x10^{-6}$ (*i.e.*, 2 μM) vitamin C were more effective than either vitamin alone. (Sato *et al.* at page 1179.) Applicants respectfully submit that neither of these concentrations are within the concentration ranges recited in present claims 57 and 67. Indeed, they are each at least 20 times less than the minimum amounts recited in present claims 57 and 67. Furthermore, Sato *et al.* discloses that use of vitamin C at 200 μM is toxic. (Sato *et al.* at page 1182.)

In essence, the Office has asserted that it would have been obvious to increase the amounts of vitamins C and E disclosed in Example 10 of the '703 patent, and supported that assertion with a disclosure that suggests that, to treat oxidative stress, one should use concentrations of vitamins C and E that are less than the amounts present in the composition of Example 10. Applicants respectfully submit that Sato *et al.* fails to support the Office's assertion that it would have been obvious to increase the amount of vitamin E and/or vitamin C in the composition of Example 10 of the '703 patent. Rather, Applicants submit that, had one looked to the disclosure of Sato *et al.*

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

in an effort to obtain guidance on modifying the composition of Example 10 of the '703 patent so that it would be suitable for treating oxidative stress, that person would have been motivated to decrease the amounts of vitamins C and E. In other words, Applicants submit that Sato *et al.* teaches away from increasing the amounts of vitamins C and E in the composition of Example 10 of the '703 patent.

Because the combined teachings of the '703 patent and Sato *et al.* teach away from the methods of present claims 57 and 67, Applicants respectfully submit that the motivation provided by the Office for increasing the concentrations of vitamins C and E in the composition of Example 10 of the '703 patent is not supported by the cited references. Thus, the Office has failed to set forth a *prima facie* case of obviousness of claims 57 and 67. Accordingly, Applicants respectfully request that the Office reconsider and withdraw the rejection of claims 57 and 67 under 35 U.S.C. § 103(a) over the '703 patent in view of Sato *et al.*

C. The '703 Patent in View of Niki (1986)

The Office maintains its rejection of claims 57 and 67 over the '703 patent in view of Niki. The Office relies on the '703 patent for the disclosure discussed above. The Office relies on Niki for the disclosure that vitamin A [*sic*, E] and vitamin C interact synergistically to decrease oxygen toxicity, and thus the occurrence of various diseases and disorders. Based on these disclosures, the Office asserts that it would have been obvious to one of ordinary skill in the art to treat oxidative stress with the composition of Example 10 of the '703 patent, as modified by the Office to comprise "greater doses of vitamins", "with the motivation of maintaining high

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

concentrations of vitamins C and E". (Final Office Action at page 4.) Applicants respectfully traverse this rejection.

Present claims 57 and 67 have been discussed above, as has the disclosure of the '703 patent.

Niki reviews the state of the art in 1986 with respect to interactions between vitamins C and E. Niki summarizes data showing that vitamins C and E can interact to inhibit oxidation. However, Niki provides no data relating to amounts of vitamins C and E to use to treat oxidative stress and disorders and diseases associated with oxidative stress. In other words, Niki neither discloses nor suggests appropriate amounts of vitamins C and E for treating oxidative stress or diseases or disorders associated with oxidative stress. Thus, even if one were to look to the disclosure of Niki in an effort to obtain guidance on modifying the composition of Example 10 of the '703 patent so that it would be suitable for treating oxidative stress and/or disease or disorders associated with oxidative stress, that person would have found no disclosure or suggestion to help him in his efforts.

As discussed above, the '703 patent provides no motivation to alter the amounts of vitamins C and E in the composition of its Example 10. Moreover, the '703 patent provides no motivation to alter the amounts of vitamins C and E in the composition of its Example 10 to achieve the controlled ratio and plasma concentration recited in present claims 57 and 67, and disclosed on page 7, lines 22-24 of the present specification. The specification states that the present invention is based on the notion that a certain ratio between vitamin C and vitamin E is necessary for optimum protection of LDL particles. (See the present specification at page 7, lines 22-24,

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

for example.) Accordingly, in order to render obvious present claims 57 and 67, the prior art must recognize the importance of the controlled ratio. See MPEP § 2144.05. Applicants respectfully submit that neither the '703 patent nor Niki recognizes this importance.

In accordance with the discussion above with regard to the '703 patent, in order to set forth a proper *prima facie* case of obviousness of claims 57 and 67, the Office must show that one would have been motivated to increase the amount of vitamin E from amount disclosed in Example 10 of the '703 patent to an amount within the range recited in claims 57 and 67. Applicants respectfully submit that the Office has not shown such a motivation.

In the absence of a showing of motivation to achieve the concentration ranges of vitamins C and E recited in the present claims, the Office has failed to set forth a *prima facie* case of obviousness. Therefore, Applicants respectfully request that the Office reconsider and withdraw the rejection of claims 57 and 67 under 35 U.S.C. § 103(a) as unpatentable over the '703 patent in view of Niki.

III. *Conclusion*

For at least the reasons set forth above, in addition to the arguments previously submitted during the prosecution of this application, Applicants submit that the cited references, alone or in combination, fail to render the presently claimed invention obvious. Thus, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 38-73, and allowance of this application.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

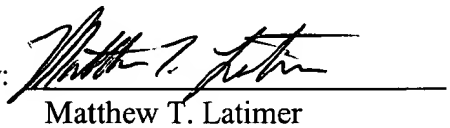
1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

If the Office believes anything further is necessary in order to place this application in even better condition for allowance, Applicants request that their undersigned representative be contacted at the telephone number or e-mail address below to discuss the remaining issues.

Please grant any extensions of time required to enter this Request, and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: 

Matthew T. Latimer
Reg. No. 44,024
(202) 408-4495
matthew.latimer@finnegan.com

Date: July 1, 2002

Attachments:
Certified Copy of Priority Document
Petition for Extension of Time

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com